so as to depend on claim 12. New claims 80 and 81 have been added and are respectively supported by claims 1 and 26 as originally filed in the priority application. Thus, after entry of the amendments, claims 1-33 and 66-81 will be pending and subject to examination.

The specification has also been amended on page 4, line 22; page 5, lines 2, 6, 17 and 20; page 6, line 22; and page 31, line 25 to correct grammatical or typographical errors. The specification has been amended on pages 24 and 25, to identify the oligonucleotides in Tables IV and V by their corresponding sequence identification numbers. The sequence identification numbers are correctly identified in the sequence listing as filed. The amendment to the specification on page 27, line 19 has been made to indicate that the initiation codon ATG is the second to fourth nucleotides of oligonucleotide 016 (SEQ ID NO:55). The amendment is supported on, for example, page 28, line 8. The amendment on page 36 indicating the simultaneous incorporation of heavy and light chain encoding fragments is supported on, for example, page 36, lines 15-16. The specification has been amended on page 38, line 29 by inserting "SEQ ID NO:76" to comply with the sequence listing requirements. A substitute sequence listing and computer readable disk are enclosed herein.

The amendments to the claims and specification do not raise an issue of new matter. Therefore, entry of the amendments to the specification respectfully is requested.

REJECTIONS UNDER 35 U.S.C. § 112

The specification stands objected to and claims 1 to 33 and 66 to 79 stand rejected under 35 U.S.C. § 112, first paragraph. Applicant respectfully traverses this ground of rejection for the reasons which follow.

The Office Action alleges that the disclosure is enabling only for claims limited to the specific construction, expression and screening of antibody fragments on the surface of M13 and to the cloning of heavy and light chain sequences without restriction sequences, as disclosed in the Examples. It is alleged that these examples are not representative of the breadth of the claims as the claims relate to any fragment, mutant or variant of a polypeptide which has the same biological activity as the disclosed antibody fragments.

Regarding claims 9-33, 66-75, 78 and 79, Applicant respectfully contends that these allegations are not relevant to the invention as claimed. Regarding claims 9-15, the invention as claimed is directed to a kit comprising two vectors. The invention as claimed in claims 16-25 and 78 is directed to a cloning system comprising two sets of vectors. Each vector recited in claims 9-25 and 78 has two pairs of restriction sites and a cloning site. The vectors are used for expression of DNA sequences inserted into the cloning sites. In addition, the invention as claimed in claims 26-33 and 79 is directed to a plurality of expression vectors. The vectors contain DNA sequences operatively linked to at least one encoding gene.

Regarding claims 66-75, the invention is directed to a vector. The vector of claims 66-70 comprises two copies of a gene encoding a filamentous phage coat protein. The vector of claims 71-75 comprises sequences necessary for the coexpression of two or more DNA sequences and also comprises two copies of a gene encoding a filamentous bacteriophage coat protein. Thus, contrary to the assertions in the Office Action, the claimed invention is not directed to a protein or polypeptide. Therefore, Applicant submits that this ground of rejection is not relevant to the invention as claimed in claims 9-33, 66-75, 78 and 79 and respectfully requests it to be withdrawn.

To practice the invention as claimed, all that is necessary is to express heteromeric receptors and screen them for a particular binding activity as described and claimed. Applicant exemplifies such methods and compositions using populations of heavy and light chain fragments to produce populations of antibody heteromeric receptors. However, the invention as claimed can be practiced with any two populations of DNA sequences encoding populations of polypeptides that interact to form heteromeric receptors other than antibodies. For example, the claimed invention can be practiced with a variety of other populations of DNA sequences within first or second gene families, which encode polypeptides that are known to form heteromeric receptors. As taught in the specification, such heteromeric receptors include, for example, T cell receptors, integrins, hormone receptors or transmitter receptors (page 5, lines 14-23).

Heteromeric T cell receptors, for example, can be produced from a first population of diverse DNA sequences within a first (TCRα) gene family, in combination with a second population of diverse DNA sequences within a second (TCRβ) gene family. Such TCRα and TCRβ polypeptides were well known in the art to form heteromeric T cell receptors. Thus, the invention can be practiced, for example, with a first population of DNA sequences within the TCRα gene family and a second population of DNA sequences within the TCRβ gene family.

Similarly, the invention can be used to construct a diverse population of heteromeric MHC class II molecules, which were well known in the art to be formed from α and β subunit polypeptides. Using a first population of diverse DNA sequences within the α subunit gene family and a second population of diverse DNA sequences within the β subunit gene family, one can readily combine these sequences to produce a diverse population of MHC class II molecules. In the same manner, the invention can be used to produce other diverse populations, such as diverse populations of integrin receptors, hormone receptors or transmitter receptors, which were known to be heteromeric receptors formed from first and second polypeptides.

Heteromeric receptors other than TCRs and MHC molecules can similarly be used in the claimed compositions and methods of the invention. All that is necessary is for the subunits to be known to assemble and form heteromeric receptors. Applicant provides sufficient guidance for the use of such molecules to enable those skilled in the art to practice the invention as

claimed. Applicant therefore respectfully requests that this ground of rejection be withdrawn.

Claims 1 and 16 stand rejected under 35 U.S.C. § 112, second paragraph. It is alleged that the term "diverse," is a relative term and, therefore, unclear. Applicant respectfully points out that "diverse" is defined in a general dictionary as "differing from one another" or composed of distinct or unlike properties. For example, the diverse combinations of first and second DNA sequences recited in claim 1 are combinations of heteromeric receptor sequences that are different from one another. Moreover, Applicant teaches the construction of a diverse population of antibody sequences which are derived from, and therefore approximate, the antibody repertoire. In light of the meaning of the term diverse and the teachings in the specification as to what constitutes a diverse population, Applicant contends that the meaning of this term is not ambiguous and unclear. According, it is respectfully requested that this rejection be removed.

Claims 4, 5, 19, 20, 29 and 30 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office Action states that the recited term "functional portions" is confusing and that it is unclear what Applicant regards as the claimed invention.

Applicant contends that the term as used in the claims is sufficiently clear to enable one skilled in the art to practice the invention. As disclosed in the specification on

page 5, lines 17-19, the term "functional portions" refers to those subunit fragments of heteromeric receptors whose assembly of the polypeptides and function of the assembled complex is retained. The specification further teaches that the variable region and Fab fragments are functional portions of antibody heteromeric receptors. Thus, as recited in the claims, Applicant contends that the objected term is not confusing or unclear. According, it is respectfully requested that this rejection be removed.

Claims 9-15 also stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite. In this regard, the Office Action states that the term "useful" is relative and that it is unclear if Applicant intended to describe the kit with a qualifier or if the term is intended for some other aspect of expression.

Applicant contends that the term as used in the claim is sufficiently clear to enable one skilled the art to practice the invention. The term useful means that the claimed vectors can be used for, or, are suitable for expressing DNA sequences which encode heteromeric receptors. However, since the claimed vectors are "useful for", they do not have to only be used for the expression of DNA sequences encoding heteromeric receptors. Rather, the vectors can be used for the coexpression of any two DNA sequences encoding polypeptides. Therefore, to further clarify Applicant's claimed invention, claim 9 has been amended so that it is directed to vectors for the coexpression of two or more DNA sequences. Applicant respectfully submits that since

claim 9, as amended, no longer recites the term objected to by the Examiner, the claim cannot be vague. Therefore, this ground of rejection is requested to be withdrawn.

Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, because the claim allegedly recites the term "expression polypeptides" without antecedent basis. This term has been replaced by the term "coexpression" to recite a proper antecedent basis. Accordingly, in light of this amendment, Applicant respectfully requests that the rejection of claim 11 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, because the claim recites the phrase "cloning site for containing." It is alleged that this phrase is confusing and unclear.

Applicant notes that claim 5 does not recite this phrase directly. However, this phrase is recited in claim 1, upon which claim 5 depends. The purpose of the cloning site recited in claim 1 is to harbor the first and second DNA sequences. Nevertheless, Applicant has deleted the word "containing" so that the claim now recites that the cloning site is for the first and second DNA sequences. The claim, as amended, is believed to be sufficiently clear to enable one skilled the art to practice the invention. Accordingly, Applicant respectfully requests that the rejection of claim 5 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim 6-8, 22-24 and 31-33 stand rejected under 35 U.S.C. § 112, second paragraph. It is alleged that these claims are confusing because they do not indicate a functional relationship between the recited bacteriophage and the cells producing them.

Applicant draws the Examiner's attention to the fact that claims 6, 22 and 31, respectively, depend on claims 77-79. Claims 77-79 each recite that the vectors are filamentous bacteriophage produced from the claimed procaryotic cells. Applicant contends that the relationship between the bacteriophage and the cells are clear since the bacteriophage are produced by the cell composition. However, if there is an alternative interpretation between the bacteriophage and the cells producing them, Applicant invites the Examiner to clarify the exact issue of concern. Accordingly, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim 26 and its dependent claims 27-33 and 79 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In this regard, the Office Action states that claim 26 is confusing for reciting the term "possible."

Applicant contends that the term as used in the claim is sufficiently clear to enable one skilled the art to practice the invention. The term possible means that the claimed plurality of first and second DNA sequences are the sequences

which encode the diverse populations of first and second polypeptides.

The Office Action also states that claim 26 is confusing by claiming a plurality of polypeptides forming a single receptor which binds a single molecule. Applicant contends, however, that the language as recited in the claim is sufficiently clear to enable one skilled the art to practice the invention. Applicant is not claiming a plurality of polypeptides which form a single receptor. Instead, Applicant is claiming a plurality of polypeptides which form a plurality of receptors. However, only one of the receptors within the population is claimed to exhibit binding activity toward a preselected molecule. Applicant teaches throughout the application the construction of diverse populations of receptors which exhibit diverse binding activities and their screening to identify at least one receptor within the population which exhibits binding activity toward the preselected molecule.

The Office Action also states that claim 26 is confusing by claiming "operable" linkages to genes. Applicant contends, however, that the language as used in the specification and recited in the claim is sufficiently clear to enable one skilled the art to practice the invention. For example, the specification describes on page 7, lines 1-17, that the expression of heteromeric receptors can be accomplished using vectors such as those described in the Examples and that such vectors contain the encoded antibody fragments functionally linked to expression elements. On page 8, lines 17-31, the

specification describes that at least one of the vectors contains, in addition to expression elements, a sequence encoding the pseudo-wild type gVIII product downstream and in frame with the cloning sites. Moreover, on page 19, line 24 through page 20, line 22, and on page 26, line 32 through page 27, line 8, the specification describes vectors for the cloning and propagation of heavy and light chain populations and for their random joining and subsequent surface expression of antibody fragment populations. Described therein are sequences and cloning sites for coat protein fusions to be constructed as well as sequences necessary for expression such as a promoter, signal sequence and translation initiation signals. These descriptions in the specification of genes, expression elements and in frame cloning sites which are functionally linked to enable the surface expression of heteromeric receptors are sufficiently clear to those skilled in the art to understand that the claimed sequences are linked so that they are operable. In light of these descriptions, Applicant therefore respectfully requests that the rejection of claim 26 and its dependents under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim 66, 67 and 70-72 stand rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that these claims are unclear in that the terms "capable of" and "substantially," are relative terms which do not have a single or unambiguous meaning.

Applicant contends that "capable of" as recited in the claims is not a relative phrase and is sufficiently clear to

enable one skilled the art to practice the invention. As recited in claims 66 and 71, the term "capable of" is intended to mean that one of the two claimed gene copies can be operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor. This ability to be operationally linked is due to the stop condon between the heteromeric receptor cloning site and the pseudo-wild type coat protein sequence which allows the heteromeric receptor to be expressed as a fusion protein on the surface of the filamentous bacteriophage or as a soluble protein. Therefore, the copy of the bacteriophage coat protein capable of being operationally linked will depend on whether the stop codon is used to unlink expression or whether it is suppressed to produce a fusion protein. Such teachings are provided in the specification on, for example, page 8, line 32 through page 9, line 16. In light of such teachings, Applicant contends that the meaning of the term is sufficiently clear to those skilled in the art.

Regarding the term "substantially," Applicant contends that one skilled in the art would know when two sequences are similar enough to be "substantially" the same. In contrast to the assertions in the Office Action, the term substantially does have a single art meaning. As defined in the dictionary, the term is recognized as meaning "being largely but not wholly that which is specified." Thus, for the claimed amino acid and vector sequences it is understood by those skilled in the art that the term includes minor modifications which do not affect function. In light of this recognized meaning, Applicant contends that the

term is clear to those skilled in the art and respectfully request that the ground of rejection be withdrawn

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1, 9, 16, 66 and 71 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Huse et al. (1989). In addition, claims 1, 9, 16, 66 and 71 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by either of the two publications to Parmley and Smith (1988 or 1989). Applicant respectfully traverses the rejections. Because the grounds of rejection under § 102(a) and § 102(b) are similar, Applicant will respond to these rejections together. The Office Action alleges that the Huse et al. and the Parmley and Smith publications each teach the limitations of claims 9-15, including vectors for the coexpression of two or more DNA sequences encoding polypeptides expressed as fusion peptides on the surface of cells.

Claims 9-15 are directed to a kit containing two vectors. Each of the vectors has two pairs of restriction sites symmetrically oriented about a cloning site. The orientation of the pairs of restriction sites within both vectors is identical. Neither Huse et al. nor Parmley and Smith teach such a pair of vectors having the claimed number and orientation of restriction sites.

Instead, Huse et al. teach a pair of vectors having antisymmetric restriction sites that flank the cloning site. The

antisymmetric restriction sites are described in Huse et al. on page 1276, second column).

The Parmley and Smith references do not even teach two vectors with restriction sites oriented about a cloning site, much less a particular number and orientation of such restriction sites. Instead, these references merely describe vectors having a cloning site (page 310, Figure 1 of Parmley and Smith, 1988). Absent any teaching of Applicant's claimed number of vectors having the claimed number and orientation of restriction sites in each vector, the cited references cannot anticipate the claimed invention. Therefore, Applicant respectfully requests that these grounds of rejections be withdrawn.

In addition, Applicant notes that the Office Action provides no basis for the rejection of claims 1, 16, 26, 66 and 71 as rejected under 35 U.S.C. § 102(a) as being anticipated by Huse et al. or as rejected under 35 U.S.C. § 102(b) as being anticipated by either the 1988 or 1989 publications of Parmley and Smith. Applicant nevertheless points out that, like claims 9-15, claims 1 and 16 similarly recite that the claimed cells and cloning system have or are derived from two vectors each having two pairs of restriction sites symmetrically oriented about a cloning site. Thus, for the reasons previously stated, neither Huse et al. nor the Parmley and Smith references can anticipate the invention as claimed in claims 1 and 16.

Moreover, in regard to claim 1, this composition is further directed to a plurality of cells having one or both

polypeptides of a heteromeric receptor expressed on the surface of the cells or bacteriophage. Neither Huse et al. nor Parmley and Smith describe both the surface expression of polypeptides and that those polypeptides form heteromeric receptors. Absent such a teaching, the cited references cannot anticipate the plurality of cells of claim 1.

Furthermore, claims 66 and 71 are each directed to vectors comprising two copies of a gene encoding a filamentous bacteriophage coat protein. The Huse et al. reference does not teach a vector containing even a single copy of a gene encoding a filamentous bacteriophage coat protein. Instead, Huse et al. teach the bacteriophage λ vector which does not contain a coat protein (page 1276, Figure 1). The Parmley and Smith references describe vectors containing only a single copy of a gene encoding a filamentous bacteriophage coat protein. The protein described by Parmley and Smith is the pIII gene product of filamentous bacteriophage (see, for example, page 306, column 1 of Parmley and Smith, 1988). Absent such a teaching of two coat proteins, one of which can be operationally linked to a DNA sequence for surface expression of a fusion protein as presently claimed, the cited references cannot anticipate the invention of claims 66 and 71. Accordingly, Applicant respectfully requests that all grounds of rejection under 35 U.S.C. § 102 be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-5, 16-21, 25-30, 66 and 71 stand rejected under 35 U.S.C. § 103 as allegedly obvious over the combination

of Huse et al. and Ladner. The Office Action alleges that the claimed invention differs from Huse et al. in that the receptor protein is expressed on the surface of a host cell in the claimed invention while being confined to the host cell cytoplasm in Huse et al. It is further alleged that the Ladner reference teaches such surface expression. Applicant respectfully traverses the rejection.

Claim 1 is directed to a plurality of cells which express heteromeric receptors on the surface of a cell or bacteriophage. The heteromeric receptors are expressed on the surface by expressing one or both of the polypeptides which form the heteromeric receptor as a fusion protein on the bacteriophage or cell surface. The specification teaches that expression of at least one of the two polypeptides which form a heteromeric receptor is sufficient for assembly of both chains on the cell surface as a functional heteromeric receptor. Claim 26 is directed to the vector populations which harbor the two polypeptide populations which make up the heteromeric receptors.

Neither Huse et al. nor Ladner WO 88/06630 teach or suggest the surface expression of two polypeptides which form functional heteromeric receptors. Huse et al. describe the cytoplasmic expression of antibody libraries in *E. coli* whereas Ladner et al. describe the expression of single chain antibodies as fusion proteins with the gene V structural protein of phage lambda.

Similarly, neither Huse et al. nor Ladner provide the motivation to express two polypeptides on the surface of a cell or bacteriophage to achieve the surface expression of heteromeric receptors. The description in Huse et al. is directed to achieving greater diversity with the described antibody libraries so as to approach the diversity of the mammalian repertoire. There is no suggestion within Huse et al. which would motivate one to attempt surface expression of such a vast antibody repertoire. Similarly, the description within Ladner is entirely directed to the expression of single chain antibodies and not to the surface expression of receptors which assemble from two polypeptide chains. Ladner similarly provides no suggestion or motivation for combining the lambda gene V expression system for use with the antibody libraries of Huse et al. Instead, Ladner provides discussions for increasing the stability of single chain antibodies inside a cell. These discussions describe the mutation of all of some of the cysteines within the antibody variable regions so as to decrease the destabilizing effect of reduced cysteines inside a cell. Applicant therefore contends that the cited references, either alone or in combination, neither teach or suggest the claimed plurality of cells expressing heteromeric receptors on the surface.

Claims 16-21 and 25 are directed to a cloning system comprising first and second vectors having two pairs of restriction sites symmetrically oriented about a cloning site. Neither Huse et al. nor Ladner teach such vectors having the claimed number and orientation of restriction sites.

As discussed previously, Huse et al. teach a pair of vectors having antisymmetric restriction sites that flank the cloning site. The Ladner reference does not even teach two vectors with restriction sites oriented about a cloning site, much less a particular number and orientation of such restriction sites. Instead, Ladner merely describes a bacteriophage lambda vector having a cloning site (pages 7-8, and Figure 7 of Ladner). Moreover, neither reference provides a motivation for constructing vectors with the claimed number and orientation of restriction sites. Instead, Huse et al. teaches a way by using vectors with an antisymetric orientation of restriction sites. Absent such a teaching or suggestion of Applicant's claimed number of vectors having the claimed number and orientation of restriction sites in each vector, the cited references cannot render obvious the invention of claims 16-21 and 25.

Finally, claims 66 and 71 are each directed to vectors comprising two copies of a gene encoding a filamentous bacteriophage protein. In contrast, neither the Huse et al. reference nor the Ladner reference teach or suggest a vector containing even a single copy of a gene encoding a filamentous bacteriophage, much less two copies. Absent such a teaching or suggestion of two copies of a filamentous bacteriophage coat protein, the cited references, alone or in combination, cannot render obvious claims 66 and 71. Therefore, Applicant respectfully requests that these grounds of rejection under 35 U.S.C. § 103 be withdrawn.

Claims 6-8, 22-24, 31-33 and 66-79 stand rejected under 35 U.S.C. § 103 as allegedly obvious over the combination of Huse et al., Ladner and the 1988 publication of Parmley and Smith. The Office Action alleges that the claimed invention is further limited to the use of filamentous bacteriophage vector, which is shown in the Parmley and Smith reference. Applicant respectfully traverses the rejection.

Parmley and Smith do not provide that which is missing from Huse et al. and Ladner so as to teach or suggest Applicant's claimed invention. Parmley and Smith is directed to the expression of short peptides on the surface of filamentous bacteriophage. There is no teaching or suggestion in Parmley and Smith for the surface expression of two polypeptide chains which form heteromeric receptors. Moreover, since Parmley and Smith is directed to the surface expression of such short peptides as epitope libraries, there is no motivation to combine the epitope expression of Parmley and Smith with the antibody library of Huse et al. to achieve the surface expression of heteromeric receptor libraries. Absent such a teaching or suggestion, the cited references, either alone or in combination, cannot teach or suggest Applicant's claimed plurality of cells and vectors as claimed in claims 1 and 26.

In regard to the remaining claims, Parmley and Smith similarly do not provide what is missing from the primary references. For example, there is no teaching or suggestion of two vectors having a pair of restriction sites symmetrically orientated about a cloning site nor is there a teaching or

suggestion of two copies of a filamentous bacteriophage coat protein. Applicant therefore contends that the claimed invention cannot be obvious over the cited references and respectfully requests that this ground of rejection be withdrawn.

Claims 1-5, 16-21, 25-30 and 66-79 stand rejected under 35 U.S.C. § 103 as allegedly obvious over the combination of Sastry et al., Ladner and Robinson et al. It is alleged that Sastry et al. describes the claimed invention in its entirety and that Ladner and Robinson et al. teach methods needed to reduce the system taught by Sastry et al. to practice. Applicant respectfully traverses the rejection.

Applicant asserts that the combination of Sastry et al. in view of Ladner and further in view of Robinson et al. does not teach or suggest Applicant's claimed invention. Sastry et al. describe the amplification and cytoplasmic expression of an antibody heavy chain library. Except for describing the expression of the heavy chains with only a few light chain polypeptides, Sastry et al. is similar to Huse et al. described above in that this reference describes only the cytoplasmic expression of an antibody library. Ladner has been described previously.

Neither Sastry et al. nor Ladner teach or suggest the surface expression of two polypeptides which form functional heteromeric receptors. As stated above, Sastry et al. describe the cytoplasmic expression of antibody libraries in *E. coli* whereas Ladner et al. describe the expression of single chain

antibodies as fusion proteins with the gene V structural protein of phage lambda.

Similarly, neither Sastry et al. nor Ladner provide the motivation to express two polypeptides on the surface of a cell or bacteriophage to achieve the surface expression of heteromeric receptors. The description in Sastry et al. is directed to achieving greater diversity with the described heavy chain antibody library. There is no suggestion within Sastry et al. which would motivate one to attempt surface expression of such a heavy chain antibody library. Similarly, the description within Ladner is entirely directed to the expression of single chain antibodies and not to the surface expression of receptors which assemble from two polypeptide chains. Ladner similarly provides no suggestion or motivation for combining the lambda gene V expression system for use with the heavy chain antibody library of Sastry et al. Instead, and as stated previously, Ladner provides discussions for increasing the stability of single chain antibodies inside a cell.

Robinson et al. is simply directed to the recombinant expression of antibody fragments. Robinson et al. does not provide that which is missing from Sastry et al. and Ladner. There is no teaching or suggestion within Robinson et al. for any type of expression other than soluble antibody fragments and therefore Robinson et al. cannot be combined with Sastry et al. and Ladner to achieve Applicant's claimed invention. Applicant therefore contends that the cited references, either alone or in

combination cannot teach or suggest the claimed plurality of cells expressing heteromeric receptors on their surface.

In regard to the claimed kits and vectors, Applicant maintains the reasons stated previously in regard to the rejection of these claims over Huse et al. in view of Ladner and apply them equally under this ground of rejection. Briefly, the combination of Sastry et al. in view of Ladner in view of Robinson et al. does not teach or suggest the claimed number of vectors each having a pair of restriction sites symmetrically orientated about a cloning site. Nor does the combination of references teach or suggest two copies of a bacteriophage coat protein. Absent such a teaching or suggestion, the cited references, either alone or in combination, cannot render the claimed invention obvious. Accordingly, Applicant respectfully requests that this ground of rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect.

Should the Examiner have any questions, he is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,

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